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Another Look into Oxygen Supplementation in the Acute Care Setting

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Recommended Readings from the University of California at Irvine Fellows; Huawei Dong M.D., Associate Program Director

Oxygen supplementation is routinely used in the acute care setting despite minimal data to support such practice and potential for hyperoxia-induced injury. The three selected articles examine the effect of supplemental oxygen on mortality and morbidity in myocardial infarction, stroke, and the acutely ill. None of the studies found a mortality benefit with the liberal use of oxygen. Oxygen therapy also did not improve re-hospitalization rate in myocardial infarction, nor improved disability in stroke or acutely ill patients. The lack of benefit and potential harm may urge both practioners and professional societies to re-examine practice patterns and guidelines.

Ravn-Fischer A, et al. Oxygen Therapy in Suspected Acute Myocardial Infarction. *N Engl J Med* (1)

Reviewed by Ken Stern

Current clinical guidelines recommend the routine use of supplemental oxygen in patients with suspected myocardial infarction (MI), as oxygen therapy is hypothesized to increase oxygen delivery to the ischemic myocardium and limit the extent of infarct (2, 3). However, the evidence to support this practice is limited. There is concern that hyperoxia may promote coronary vasoconstriction and increase the production of reactive oxygen species. In addition in patients undergoing percutaneous coronary intervention, reperfusion generate oxygen free radicals and may increase infarct size (4). This was demonstrated in the AVOID trial (5) which randomized subjects with pre-hospital ST elevation MI and a pulse oximetry saturation (SpO2) ≥95% to oxygen at 8 L/min versus ambient air. The primary end point of myocardial infarct size was significantly larger in the oxygen group.

The DETO2X-AMI trial randomized 6629 Swedish patients with suspected MI to supplemental oxygen (6 L/min for 6 to 12 hours) versus ambient air. Eligible participants had symptoms suggestive of MI for less than 6 hours, SpO2 ≥ 90%, and electrocardiographic changes indicative of ischemia or

elevated cardiac enzymes. The primary end point of all-cause mortality at 1 year was 5.0% in the oxygen group versus 5.1% of the ambient-air group (HR 0.97; 95% CI, 0.79-1.21; p = 0.80). Secondary endpoints included 30-day all-cause mortality, rate of re-hospitalization with MI, heart failure, or cardiovascular death, as well as composites of these end points. There was no significant difference in 30-day all-cause mortality or re-hospitalization rates from MI evaluated at 30 days and 1 year.

These data suggest that the routine use of supplemental oxygen in patients with suspected MI without baseline hypoxemia does not alter 1-year all-cause mortality or incidence of re-hospitalization from MI. Compared to the AVOID trial, DETO2X-AMI randomized 15 times more subjected with broader inclusion criteria and examined endpoint such as mortality and re-hospitalization rates, making the results more clinically applicable. Weaknesses of this study include an open-label design, lack of centrally adjudicated endpoint measures, and a discrepancy between anticipated and observed 1-year mortality rates suggesting the study may be underpowered. Despite these limitations, DETO2X-AMI provides strong evidence with practical clinical endpoints that were previously lacking and creates support for changes to current clinical practice.

1. Ravn-Fischer A, Nilsson L, Hofmann R, Jernberg T, Witt N, Pernow J, et al. Oxygen Therapy in Suspected Acute Myocardial Infarction. *N Engl J Med.* 2017;377:1240–1249.
2. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J.* 2016;37:267–315.
3. O'Connor RE, Al Ali AS, Brady WJ, Ghaemmaghami CA, Menon V, Welsford M, Shuster M. Part 9: Acute Coronary Syndromes. *Circulation.* 2015;132:S483–S500.
4. Grech ED, Dodd NJF, Jackson MJ, Morrison WL, Faragher EB, Ramsdale DR. Evidence for free radical generation after primary percutaneous transluminal coronary angioplasty recanalization in acute myocardial infarction. *Am J Cardiol.* 1996;77:122–127.
5. Stub D, Smith K, Bernard S, Nehme Z, Stephenson M, Bray JE, et al. Air versus oxygen in ST-segment-elevation myocardial infarction. *Circulation.* 2015;131:2143–2150.

Roffe C, et al. Effect of Routine Low-Dose Oxygen Supplementation on Death and Disability in Adults with Acute Stroke: The Stroke Oxygen Study Randomized Clinical Trial. *JAMA* (6)

Reviewed by Shyam Rao

With the increasing incidence of cerebrovascular accidents, there has been a growing interest in hypoxia which is common after stroke (7). While oxygen is thought to provide support for the cells outside of the penumbra that are at risk for cell death, it may lead to hyperoxia-induced vasoconstriction, free radical formation, ischemia-reperfusion injury, and immobility (8, 9). Thus, evidence is needed to better delineate the risk versus benefit of oxygen supplementation in stroke patients.

This study by Roffe et al, was a multi-centered randomized clinical trial with over 8000 patients in the United Kingdom. Patients were equally randomized to one of three groups: continuous oxygen supplementation, nocturnal oxygen supplementation, and no routine oxygenation for 72 hours. The primary outcome was the modified Rankin Scale at 90 days. Secondary outcomes included neurological improvement at start and at 7 days, highest and lowest oxygen saturation, and mortality at 1 week. Assessments occurred at 7 and 90 days by postal questionnaire.

When combined oxygen therapy (continuous and nocturnal) was compared to control, there was no improvement in functional outcomes at 90 days (OR

0.97; 95% CI, 0.89 to 1.05; p=0.47). Continuous and nocturnal oxygen therapies were similar (OR 1.03; 95% CI, 0.93 to 1.13; p=0.61). Secondary outcomes also failed to demonstrate any improvement with oxygen therapy in mortality, neurologic impairment, independence, or performance of activities of daily living at 90 days.

Some limitations of the study include the use of a postal questionnaire for the primary outcomes, poor adherence, and lack of radiographical confirmation of the diagnosis. These results were in contrast to the author's original pilot study which yielded a significantly improved neurologic recovery at 1 week (10). A larger subject pool and increased parity between the groups may have led to these varying results.

The time after a stroke is crucial for the prevention of further neurologic damage. This study provides evidence to show that the traditional practice of oxygen supplementation in stroke does not reduce neurologic disability in non-hypoxic patients. In addition, ischemic-reperfusion injury and the inflammatory cascade that can result from oxygen reperfusion is a concern. Thus, oxygen therapy may not only be non-beneficial but also may be harmful in this population with existing cellular injury.

6. Roffe C, Nevatte T, Sim J, Bishop J, Ives N, Ferdinand P, et al. Effect of Routine Low-Dose Oxygen Supplementation on Death and Disability in Adults with Acute Stroke: The Stroke Oxygen Study Randomized Clinical Trial. *JAMA*. 2017;318(12):1125-1135.
7. Roffe C, Sills S, Halim M, Wilde K, Allen MB, Jones PW, et al. Unexpected nocturnal hypoxia in patients with acute stroke. *Stroke*. 2003;34(11):2641-2645.
8. Floyd TF, Clark JM, Gelfand R, Detre JA, Ratcliffe S, Guvaov D, et al. Independent cerebral vasoconstrictive effects of hyperoxia and accompanying arterial hypocapnia at 1 ATA. *J Appl Physiol*. 2003:95(6):2453-2461.
9. O'Driscoll BR, Howard LS, Earis J, Mak V, British Thoracic Society Emergency Oxygen Guideline Group, BTS Emergency Oxygen Guideline Development Group. BTS guideline for oxygen use in adults in healthcare and emergency settings. *Thorax.* 2017;72(suppl 1):ii1-90.
10. Roffe C, Ali K, Warusevitane A, Sills S, Pountain S, Allen M, et al. The SOS pilot study: A RCT of routine oxygen supplementation early after acute stroke – effect on recovery of neurologic function at one week. *PLoS One*. 2011:6(5):e19113.

Chu D, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet* (11)

Reviewed by Timmy Cheng

Supplemental oxygen is regularly administered in acutely ill patients despite normal oxygenation levels, as it is often viewed as a “harmless treatment” with potential benefits (12). However, a growing volume of observational studies and meta-analyses suggest an association between hyperoxia and increased in-hospital mortality after cardiac arrest, traumatic brain injury, and stroke (13, 14).

Chu D, et al sought to compile high-quality evidence through a meta-analysis of strictly-chosen studies. The authors conducted a comprehensive literature search from several databases, including the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, HealthSTAR, LILACS, PapersFirst, and the WHO International Clinical Trials Registry. Only randomized controlled trials that compared liberal and conservative oxygen supplementation in acutely ill patients of any condition requiring hospitalization were included in the analysis. Outcomes measured were mortality and morbidity. Mortality measures included in-hospital mortality, 30-day mortality, and mortality at longest follow up. Morbidity was defined as disability at longest follow-up,

risk of hospital acquired pneumonia, risk of any hospital acquired infection, and hospital length of stay.

A total of 25 randomized controlled trials were included in the meta-analysis, encompassing 16,037 patients admitted for critical illness, trauma, sepsis, stroke, myocardial infarction, cardiac arrest, or emergency surgery. Median fraction of inspired oxygen (FiO2) was 0.52 in the liberal oxygen group, versus 0.21 in the conservative oxygen group. Liberal oxygen supplementation was found to have increased in-hospital mortality (RR 1.21, p=0.020), 30-day mortality (RR 1.14, p= 0.033), and mortality at longest follow up (median 3 months, RR 1.10, p = 0.044). There was no difference in disability, hospital acquired infections, or hospital acquired pneumonia between the two groups.

To date, this is the most comprehensive meta-analysis of randomized controlled trials. The analysis demonstrated an increased mortality in acutely ill patients treated with liberal oxygen supplementation, and a lack of improvement in overall morbidity or disability in stroke and traumatic brain injury patients. Excessive oxygen has been shown to promote vasoconstriction, inflammation, and oxidative stress on the pulmonary, cardiovascular, and neurological systems, and this effect may be responsible for the differences seen (12, 15). Overall, this meta-analysis is consistent with prior data suggesting that liberal oxygen supplementation is linked to increased overall mortality in acutely ill patients.

11. Chu DK, Kim LH, Young PJ, Zamiri N, Almenawer SA, Jaeschke R, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet*. 2018;391(10141):1693-1705.

12. Hale KE, Gavin C, O'Driscoll BR. Audit of oxygen use in the emergency ambulances and in a hospital emergency department. *Emerg Med*. 2008;25:773-776.

13. Rønning OM, Guldvog B. Should stroke victims routinely receive supplemental oxygen? A quasi-randomized controlled trial. *Stroke*. 1999;30:2033–37.

14. Khoshnood A, Carlsson M, Akbarzadeh M, Bhiladvala P, Roijer A, Bodetoft S, et al. The effects of oxygen therapy on myocardial salvage in ST elevation myocardial infarction treated with acute percutaneous coronary intervention: The Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion (SOCCER) study. *Cardiology*. 2015;132:16–21.

15. Hafner S, Beloncle F, Koch A, Radermacher P, Asfar P. Hyperoxia in intensive care, emergency, and peri-operative medicine: Dr. Jekyll or Mr. Hyde? A 2015 update. *Ann Intensive Care*. 2015;5:1–14.